REMARKS/ARGUMENTS

The Patent Office's withdrawal of previous objections and rejections is acknowledged and appreciated. Amendments are made in claims 30 and 31 to clarify these claims. These amendments are not made in response to a patentability-based rejection, and do not add new matter. Entry of these amendments is respectfully requested.

Upon entry of these amendments to claims 30 and 31, claims 16-35 remain pending and under examination.

Rejections under 35 USC 103(a)

Claims 16-22 stand rejected under 35 USC 103(a), as being allegedly unpatentable over Ziche et al. (1997 Lab. Invest. 76(4) 517-531, hereinafter, "Ziche") and further in view of Failla et al. (2000 J. Invest. Dermatologoy 115(3): 388-395. hereinafter, "Failla").

First, it is generally noted that the target diseases of the present invention are related to alterations of the connective tissues and are characterized by fibroblast activation and excessive production and deposit of sclerosed collagen with formation of fibrosis and calcification zones. Ziche has already thoroughly been discussed in the August 17, 2005 reply/amendment to the preceding office action. Ziche discloses the ability of PLGF-1 to elicit angiogenesis in in the rabbit cornea and in the chicken chorioallantoic membrane. This is a simple biological activity developed on normal (healthy) rabbit cornea or chorioallantoic membrane.

Yet Ziche does not disclose or suggest that the pathological picture treated according to the invention is caused by or correlated to a deficient angiogenesis in the connective tissues. Actually, the biological activities shown by Ziche are not suggested to have any involvement or cause/effect relationship with alterations of the connective tissue.

Nor could the skilled reader find any suggestion in Ziche's teaching that giving heterologous PLGF-1 would improve vascularization in sclerotic connective tissues, as observed in healthy cornea, or that improved vascularization, if any, would be able to restore the healthy state of the connective tissues.
Failla et al. teaches that native PLGF is induced in human keratinocytes during wound healing and demonstrates that PLGF plays a role in the neoangiogenesis process associated with wound repair.

The first observation is that a "wound" is definitely different from the pathological states of scleroderma and the other connective tissue diseases according to the invention. Wounds are normally due to external agents, which are not comparable to the impaired metabolism resulting in the production and deposit of sclerosed collagen in the connective tissues.

Therefore, for example, "wound healing" and "scleroderma treatment" represent different therapeutic treatments. For this reason, should Faille actually suggest that PLGF may be used in the healing of wound, this suggestion, nevertheless, would be immaterial to any further, different, unrelated therapeutical use of PLGF such as is disclosed in claims 16-22.

However, apart from the above differences, Failla does not even disclose the use of PLGF in the treatment of wounds.

In fact, while indicating a role of PLGF in cutaneous wound repair process, Failla does not demonstrate nor enable that PLGF has any active function in the healing. Said in other words, the reference fails to show that the induced PLGF is the factor causing the healing rather than simply a side effect of the wound. By way of example, there are known benign tumors characterized by the release of thyroid hormones. The higher level of circulating hormones are neither the cause of the tumor nor a repair factor for the tumor damages, but simply a side effect.

Finally, Failla does not show that the PLGF induced in vivo actually is PLGF type 1, and not PLGF-2, PLGF-3 or any heterodimeric form PLGF/VEGF, such as: PLGF-1/VEGF165, PLGF-2/VEGF165, PLGF-3/VEGF165 or PLGF-1/VEGF121. In fact, this latter possibility, that the protein detected in vivo be a heterodimer PLGF/VEGF, is unambiguously indicated by Failla at page 393, line 11 left hand column.

In conclusion as to this rejection of claims 16-22, the Failla reference, taken alone or in combination with Ziche, does not appear to be able to suggest the therapeutic use of the PLGF-1 according to the invention. Reconsideration and withdrawal of the rejection of the indicated claims based on this combination of references is respectfully requested.

Claims 30-35 stand rejected under 35 USC 103(a), as being allegedly unpatentable over Carmeliet et al. (WO 015693). This earlier application describes pharmaceutical compositions comprising PLGF for the prevention or treatment of an ischemic disease. Reconsideration and withdrawal of this basis for rejection is respectfully requested for the following reasons.

First, Applicant believes that a *prima facie* case of obviousness has not been met because the Carmeliet reference does not provides some teaching, motivation or reasoning to obtain the invention as claimed in claims 30-35. The Office action simply states "It would have been obvious to a person having ordinary skill in the art to fomulate a composition comprising PLGF-1 as an active principle in dimeric form, and in an amount of about 2 to 2,000 ug per kg of body weight of subject (claims 30-35) with a suitable pharmaceutical carrier and/or agent because Carmeliet teach and suggest the use of compositions comprising PLGF-1 dimer as active principle for improving infarct angiogenesis and ateriogenesis." The Office action appears conclusory on this point, and fails to articulate a reasonable explanation that leads one to find a teaching or motivation to achieve the respective combinations of elements in claims 30-35. No teaching of the percentage limits of PLGF-1 forms in claims 30 and 31 are provided in Carmeliet, no discussion of parenteral or topical doses are provided in Carmeliet, nor is there any discussion of cosmetic compositions, and, per below, the doses are not readily or appropriately

comparable. Accordingly, neither the Carmeliet reference, nor any other evidence of record, establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Even assuming *arguendo* that a *prima facie* case of obviousness were established, there are other reasons, per below, that withdrawal of this basis of rejection is appropriate.

First of all, ischemic diseases are not comparable to scleroderma or any other connective tissue alteration. Also, the Patent Office recognizes that Carmeliet does not disclose compositions comprising PLGF in an amount of from 50μg to 30 mg per unit dose for parenteral use and from 0.1 mg to 10 mg per gram for topical use as claimed in the present application. The Patent Office, however, considers that it would have been obvious for the skilled person to prepare a composition comprising the same amount of PLGF.

The first specific observation is that the compositions according to claims 30 and 31 comprise highly purified PLGF wherein at least 98.5% of PLGF-1 is in active dimeric and multimeric form and no more of 1.5% in inactive monomeric form. A method for purifying PLGF is disclosed for instance in the PCT international application PCT/IT02/00065 (WO-A-03/066676) cited on page 5, line 29 of the international publication corresponding to the present US application. Carmeliet does not provide specific limits of the composition it used, so it is speculative as to what are the properties of the PlGF used in Carmeliet.

The amount of PLGF for unitary dosage according to the present invention is higher than the amount indicated by Carmeliet, who suggests dosages of 2 to 2000 μg per Kg of body per week. This means, for a patient of 60 Kg, 120 μg to 120 mg per week or, for a daily unitary dosage, about 17 μg to about 17 mg per daily dose. Since Carmeliet administered its dosages using an osmotic pump operating continuously (see page 14, line 3), it is not proper to directly equate the daily doses using this to a single parenteral dose as claimed herein. Particularly, the fact that Carmeliet chose to administer via a pump rather than by parenteral administration indicates a teaching away of providing parenteral doses (note in particular in Example 5 Carmeliet's concerns about hypotension, and its relatively low dosage of 5 ug PlGF for evaluation of same,

which indicate a concern about and/or an aversion to larger single parenteral doses). Therefore, it is respectfully asserted that the concentrations and levels used by Carmeliet, given the differences in forms of administration, do not fall within the claimed ranges. Accordingly, on this basis, alone or in combination with other bases provided herein, Carmeliet does not render obvious claims 30-35.

Further, it is appreciated that a higher amount of active principle in a composition is not in itself capable of endowing a claim with an inventive merit, unless this higher amount does actually reflect the optimized amount suitable to treat a specific disease. This is the case here as shown by the examples.

In fact, the examples highlight two important aspects of the treatment of the connective tissue alterations. The first is that the effect is achieved after quite long a treatment, namely daily applications for 20 to 60 days. The second is the dose/effect dependency. Example 6 and 7 make clear that in order to see a recognizable and practically useful effect, proportionally high daily amounts of medicament have to be given. Whereas below a defined daily amount, no effect can be appreciated.

Further, it is appreciated that claims 31, 33 and 35 are directed to cosmetic compositions. There is no suggestion or teaching of a cosmetic application in the Carmeliet reference (the compositions are provided via a subcutaneously implanted minipump). Nor does the 10/20/2005 Office action provide specific reasoning of how subcutaneous administration of a PLGF-containing composition for enhanced revascularization of acute myocardial infarcts would teach or suggest a cosmetic composition comprising PLGF as stated in claims 31, 33 and 35. It is respectfully asserted that the Patent Office has not met its burden to establish a prima facie case of obviousness specifically for these claims. In the alternative, it is respectfully asserted that the teachings of Carmeliet do not render obvious these claims directed to cosmetic compositions because there is no teaching or suggestion of such compositions in Carmeliet.

A further observation is that the Examiner's objection concerning the dosage amount of PLGF-1 is based on hindsight of the invention.

Accordingly, contributions of the present inventors include identification of the suitable PLGF-1 form and the suitable amounts, under the different circumstances, effective to treat in humans diseases and alterations of the connective tissues otherwise difficult to treat.

In conclusion, it seems that none of the cited documents would be able to make the claimed compositions obvious. For the reasons above, alone or in combination, reconsideration and withdrawal of the rejections to indicated claims is respectfully requested.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

* * * * * * *

The Examiner is invited to call the undersigned if clarification is needed on any aspects of this Reply/Amendment, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion. In particular, if amendment of a claim, including alteration of a claim style to a style more commonly found in U.S. patent applications, may be viewed to advance this application to allowance status, the courtesy of a telephone call to the undersigned toward such amendment will be most appreciated.

Respectfully submitted,

1/19/2006

Joseph Fischer
Patent Attorney, Registration No. 51,210
(Customer No. 29,391)
Mailing Address and Phone/Fax numbers:
Beusse Wolter Sanks Mora & Maire, P.A.
390 N. Orange Avenue, Suite 2500
Orlando, FL 32801
Telephone: 407-926-7727
Fax: 407-926-7720